342/78

G.P.-S.51994—1976-77—3 000 (P) J 219

In the Supreme Court of South Africa
In die Hooggeregshof van Suid-Afrika

(Appellate ~~Provincial~~ - Division)
(........................ ~~Provinsiale~~ Afdeling)

Appeal in Civil Case
Appèl in Siviele Saak

The B-M Group (Pty) Ltd .... *Appellant,*

versus

Beecham Group Limited .... *Respondent*

Appellant's Attorney
Prokureur vir Appellant ....

Respondent's Attorney
Prokureur vir Respondent ....

Appellant's Advocate
Advokaat vir Appellant ....

Respondent's Advocate
Advokaat vir Respondent ....

Set down for hearing on
Op die rol geplaas vir verhoor op ....

(T.P.D.)

Coram: ....

Vir Appellant ....

Vir Respondent ....

UITSPRAAK ....

Writ issued Lasbrief uitgereik..........	Bills taxed - Kosterekenings getakseer		
	Date Datum	Amount Bedrag	Initials Paraaf
Date and initials Datum en paraaf..........			

IN THE SUPREME COURT OF SOUTH AFRICA

(APPELLATE DIVISION)

In the matter between:

THE B-M GROUP (PROPRIETARY) LIMITED ..... Appellant

AND

BEECHAM GROUP LIMITED ..... Respondent.

Coram: TROLLIP, CORBETT, MILLER, VILJOEN, JJ.A. et GALGUT, A.J.A.

Heard: 19 - 23 May 1980.

Delivered: 2 September 1980.

J U D G M E N T

TROLLIP, J.A. :

INTRODUCTION

This appeal concerns the validity and the alleged infringement of a South African Patent, No. 63/4795, entitled "Penicillins". It is a convention patent granted under the Patents Act No. 37 of 1952 ("the Act") on 15 July 1964 with an effective or priority date of 2 November 1962. (It was common cause that, despite the repeal and replacement of the Act by Act No. 57 of 1978, its provisions are still applicable to these proceedings.) The registered proprietor of the patent is the respondent, Beecham Group Limited ("Beecham"). This company carries on business in England as a manufacturer and seller of inter alia ethical pharmaceutical preparations. During the pendency of this appeal the patent expired. We were informed from the Bar,

however .... /3

however, that proceedings are afoot for its extension.

The appellant ("Bristol") is the virtually wholly owned South African subsidiary of Bristol-Myers Incorporated, a U.S.A. company or group of companies, which carries on a similar kind of business to that of Beecham.

In December 1975 Beecham sued Bristol in the Court of the Commissioner of Patents in Pretoria for infringement of the patent. It claimed an interdict, an inquiry into damages, and costs. Bristol defended the action. It alleged that the patent was invalid on the grounds that (a) the invention claimed was not new; (b) it was obvious, involving no inventive step; (c) it was not useful; and (d) neither it nor its manner of performance was fully described and ascertained in the specification. Bristol also counterclaimed for the revocation of the patent on

the .... /4

the same grounds. The only two grounds that were ultimately canvassed before us were (b) - obviousness, and (c) - utility. The other grounds, as well as other issues raised on the pleadings and during the proceedings, fell away before or during the course of the present appeal. They need therefore not be detailed or dealt with.

The learned Commissioner, NICHOLAS, J., found for Beecham on its claims in convention and against Bristol on its counterclaims, and issued the appropriate orders inter alia for an interdict, investigation of damages, and costs. The Full Bench of the Transvaal Provincial Division (IRVING STEYN, MCEWAN, and FRANKLIN, JJ.) dismissed Bristol's appeal with costs, but granted it leave to appeal to this Court.

BRIEF HISTORICAL BACKGROUND

The .... /5

The name "penicillin" comes from penicillium meaning mould. According to the evidence Sir Alexander Fleming first discovered the anti-bacterial activity of a naturally produced mould or fungus in 1928. Thereafter many penicillins were produced for therapeutic use against various bacteria. These were natural penicillins derived from moulds produced by fermentation, a purely biological process. As Professor Rinehart, Professor of Chemistry (including antibiotics) of the University of Illinois, U.S.A., said:

> "the penicillin chemistry has always been an exciting field for antibiotics chemists; penicillin was among the first antibiotics isolated and really led to the wonder drug era .... there's always been excitement associated with it ..."

Beecham first decided to enter the penicillin field in 1956. Dr Nayler, now its senior organic chemist, was

deputed .... /6

deputed to supervise the chemical research aspects of the project. He was the co-inventor of the penicillins under inquiry in these proceedings. He testified that, when he started his researches, he found well over 100 natural penicillins mentioned in the relevant literature. The vast majority of them were said to be active against "Gram-positive" bacteria but had little activity against "Gram-negative" bacteria. (These terms will be explained presently.) Those that were better known and are relevant here are Penicillins N, G, and X. The difficulty with natural penicillins was that they were not acid stable. They were therefore unsuitable for oral administration in humans since stomach acids precluded the dosage from having its full, desired effect. The more effective way of administering them was by subcutaneous injection. That was not always convenient, possible, or popular.

Moreover .... /7

Moreover, and of greater significance, the kinds of penicillins were limited to those producible by fermentation. That inhibited the synthesizing chemically of a wider range of penicillins with different or better properties.

However, in 1957 Beecham, through Dr Nayler and his co-researchers, discovered and isolated the nucleus common to all penicillins: 6 -amino-penicillanic-acid or (abbreviated) 6 -APA. According to NICHOLAS, J., this was a "brilliant, seminal discovery". Professor Rinehart proclaimed it "a very exciting development .... a matter of great interest .... a major break-through." The discovery was patented. It meant that a much wider variety of penicillins, hitherto inaccessible, could now be synthesized by simply coupling other chemical groups to the nucleus, 6 -APA. And it was along those lines that Beecham's

further .... /8

further researches were then directed. It wanted to explore the whole area of penicillins, to make and test many diverse kinds, and to determine their respective properties. Its top priority was to find new penicillins that were active against certain Gram-positive bacteria, like staphylococci, that had become resistant to existing penicillins. This had caused appreciable problems in hospitals and medical practice. These problems were much ventilated in the press at the time. We are not concerned here with that particular line of investigation. But Beecham was also interested in finding penicillins that were acid stable and active against Gram-negative bacteria. We are concerned with these problems, especially the latter. Hitherto the only natural penicillin that had shown any such activity was Penicillin N. This consequently became Beecham's "lead compound" for this latter

purpose .... /9

purpose. Its chemical structure afforded guidance to the kind of analogues that should first be researched. Beecham regarded it as "a unique pointer" in that respect.

In its early researches undertaken after the isolation of the nucleus, 6 -APA, Beecham made the further interesting and encouraging discovery that, by substituting the amino group in the alpha position in the side-chain of the nucleus 6 -APA (all to be explained presently), the resultant penicillin was acid stable. That was an appreciable advance towards producing orally effective penicillins. In particular, Penicillin N was not acid stable and was therefore unsuitable for oral administration.

Beecham's further researches and discoveries led to its applying on 6 October 1958 in South Africa and in 1959

in .... /10

in England for a further patent to cover the new penicillins.

The S.A. patent was granted on 24 August 1960. It was referred to in the present proceedings as "the 1959 Patent". The title was "Improvements in or relating to Penicillin Derivatives".

The essence of the invention was the coupling to the previously isolated nucleus 6 -APA of multifarious amino-acyl substituent groups according to a general formula in order to produce the penicillin derivatives that were claimed in the specification. It was common cause that theoretically the compounds covered by the specification could amount to at least several hundreds of thousands. The patent expired in September 1975. Its validity was not in issue in these proceedings. The most successful of its products was marketed from July 1961 under the trade name of "ampicillin". Beecham was granted a separate patent for it.

Following .... /11

Following upon its further researches and discoveries Beecham applied on 22 October 1963 for the patent in suit, No. 63/4795. As already mentioned it was granted on 15 July 1964 with an effective date of 2 November 1962. It was referred to in these proceedings as "the 1963 Patent". The specification refers to the 1959 Patent and its wide general formula. It alleges that Beecham had found certain compounds (6 or possibly 9) that fell within that general formula and which "have particularly desirable properties especially in respect of their activity against Gram-negative bacteria". It was common cause that these compounds, although not specified in the 1959 Patent, theoretically fell within its very wide ambit. Indeed, Bristol pleaded inter alia that the invention claimed under the 1963 Patent lacked novelty for, so it was alleged, it had been claimed or described

by .... /12

by the 1959 Patent. This averment was rejected by both the Courts below and it was not pursued before us. One of the penicillins claimed in the 1963 Patent (trade-named "amoxycillin") subsequently proved to be a highly successful antibiotic. Beecham alleged, and Bristol admitted, that it was this penicillin that Bristol had manufactured and was selling or intended to sell. Beecham applied for a separate patent for amoxycillin in 1969. It is not in issue in these proceedings.

GLOSSARY OF TECHNICAL TERMS AND INFORMATION

Following the helpful example set by the Court a quo I interpolate here a glossary of some of the relevant technical terms and information. Much of it is taken from Professor Rinehart's helpful report and evidence on the techinical aspects of the case.

(1) .... /13

(1). An antibiotic is a chemical compound produced by one micro-organism which in dilute concentration inhibits the growth of or kills another micro-organism. The chemistry of antibiotics is one of the narrower, albeit important and active, fields of chemistry. Within that field penicillin chemistry is a specific, important, and exciting area.

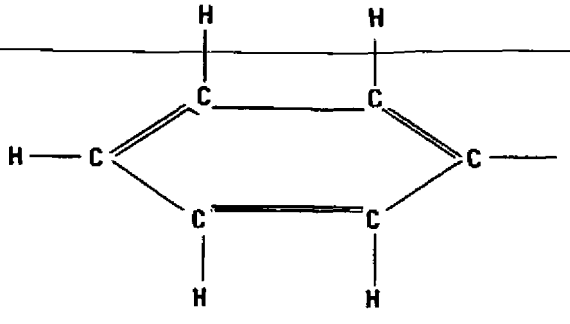
(2). A chemical compound is formed when various atoms become bonded together to form a molecule. It is often described by the use of a formula. Its structural formula indicates the arrangement of the atoms in the molecule. The bonds or valencies between them are represented by straight lines (single or double lines as the case may be), and the atoms by their recognized abbreviations: for example, C is carbon, H hydrogen, O oxygen, and N nitrogen. Where more than one atom is involved, that is

indicated .... /14

indicated by the appropriate numeral, thus, H_2O, or CH_3. Sometimes a single bond or valency is simply signified by a dot instead of a line. Thus, $CH_2.CO$ instead of CH_2-CO.

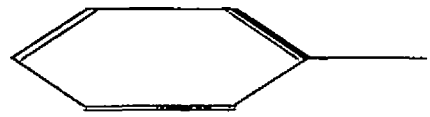
(3). A group or radical is a sub-part of a molecule formed by a particular combination of atoms. A common group or radical is usually assigned a name by which it is conveniently known. Relevant examples follow.

(4)(i). A common group is the aryl of which the best-known and simplest is the phenyl group. In the latter group six carbon atoms are bonded together in a hexagonal arrangement with alternating double bonds between them. Its simple structural formula is:



The .... /15

The single, unattached line at the right-hand end of the group is the bond by which the group is attached to the other part of the molecule. Since this group is so well-known its structural formula is often condensed and simplified thus:



This is also known as the phenyl ring.

(ii). Benzyl Group is the phenyl ring, with the alkyl radical, CH_2-, attached to its right-hand valence. This is also known as the benzyl ring.

(iii). Hydroxy or Hydroxyl Group. Its formula is HO- or OH-. It is derived from the carboxylic acid group, -COOH.

(iv). Acyl Group. Its formula is -CO-, being also derived from the carboxylic acid group, COOH, by the removal of the hydroxy group, OH, therefrom.

(v) .... /16

(v). Amino Group. Its formula is NH_2 or H_2N. Any organic compound containing this group and the carboxylic acid group, COOH, is an amino acid.

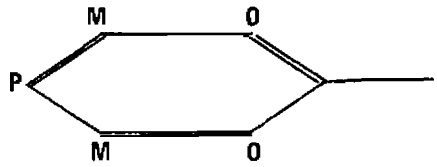
(vi) Amino-acyl Group indicates a group which in itself contains the amino, NH_2, and the acyl radical, CO. The essence of the 1959 Patent was the introduction of amino-acyl substituent groups into the amino group of the penicillin nucleus, 6 -APA, in order to obtain the multifarious penicillin derivatives. See the discussion of the 1959 Patent infra.

(5). Ortho, meta, and para positions. These are the conventional names of the different positions in which a substituent, for example the hydroxy group, HO, can be attached to the phenyl ring at any one of three points. The corresponding abbreviations are the o, m, and p positions. There are two equivalent ortho

positions .... /17

positions, two equivalent meta positions, and one para position.

Thus -



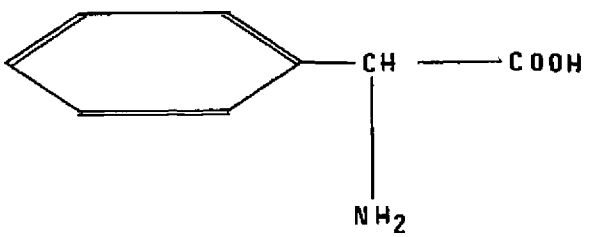
The hydroxy substituent group can be attached at any of those positions to become the ortho -, meta -, or para -hydroxyphenyl or o -, m -, or p -hydroxyphenyl, as the case may be. When it is required to write a formula which is generic to all three substitution positions, the bond line is drawn through one of the sides of the ring and into the centre of it, thus -

This represents each one of the three possibilities, the o -, m -, or the p -hydroxyphenyl.

(6). Alpha position. Another system of identifying points

of .... /18

of attachment is by the use of the Greek alphabet (alpha, beta, etc.) assigned to each carbon atom in the compound to which an attachment is made. We are here concerned only with the alpha position. Thus the structural formula of alpha-amino-phenylacetic acid is -

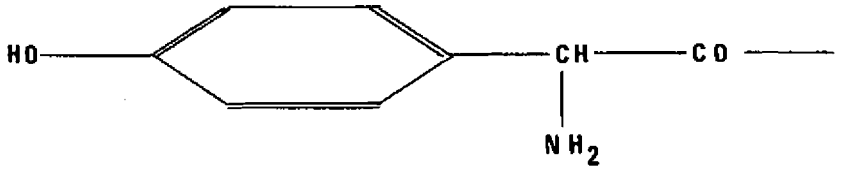


There the amino group, NH_2, is attached to the carbon atom, C, in the alpha position.

(7). Naming of compounds. The "name" of a compound is the verbalization of its formula. The use of verbal formulas or names is a practical necessity in communication since a structural formula cannot be orally and sometimes even literally reproduced. The compound is therefore named in such a way as to identify each

component .... /19

component part or radical present in the molecule and to show how they are linked together to form the molecule. For example, a penicillin claimed in the 1963 Patent is named 6 -(p - Hydroxy - α - aminophenylacetamido) - penicillanic acid. That describes a compound in which the groups coupled to the nucleus, 6 -APA, are the hydroxy group (attached to the phenyl ring in the para-position), the amino group (attached to the carbon atom in the alpha position) and the acetic acid group. The structural formula of the coupled part (side-chain) is -



(8). Gram-positive and Gram-negative bacteria. These are two categories of bacteria which are distinguished from one another by a staining test first developed and described by the scientist

Gram .... /20

Gram. Examples of the Gram-positive kind are Staphylococcus ("Staph.") and Streptococcus. Examples of the Gram-negative kind are Escherichia Coli ("Esc. Coli"), Salmonella Typhi ("Salm. Ti."), Klebsiella Pneumoniae ("Kleb. Pneu."), and Salmonella Typhimurium ("Salm. Tm."). These are fairly representative types of Gram-negative bacteria.

(9). MIC tests. These are in vitro tests, i.e., those conducted in dishes, plates, test tubes, flasks, or the like in order to ascertain the minimum concentration of the test compound that stops the test organism from growing. MIC is the abbreviation of Minimum Inhibitory Concentration. The results of tests adduced in evidence in these proceedings were given in micrograms per millilitre. The lower the number of micrograms required, the higher the efficacy of the compound.

(10) .... /21

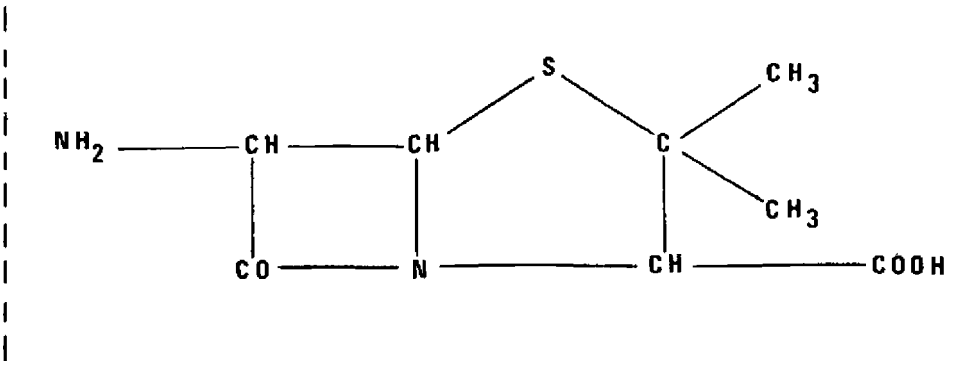
(10). CD_{50} tests. CD is the abbreviation for Curative (i.e. effective) Dose. These tests are in vivo, i.e., on live animals - in the present case on mice. CD_{50} is the notional dose taken from a graph of results showing cures in 50% of the test animals that were infected with the particular bacteria. Again, the lower the resultant number, the higher the efficacy of the test compound.

(11). AB. Every compound produced by experimentation by Beecham and submitted to testing is numbered consecutively. If it is an antibiotic the letters AB are added as a prefix. The numbers therefore indicate the chronological order in which the compounds were produced and tested.

(12). The Penicillin Nucleus, 6 -APA. This is the compound 6 - amino - penicillanic - acid, common to all penicillins. It was isolated by Beecham in 1957. Its structural formula is shown

hereunder .... /22

hereunder to the right of the dotted line:



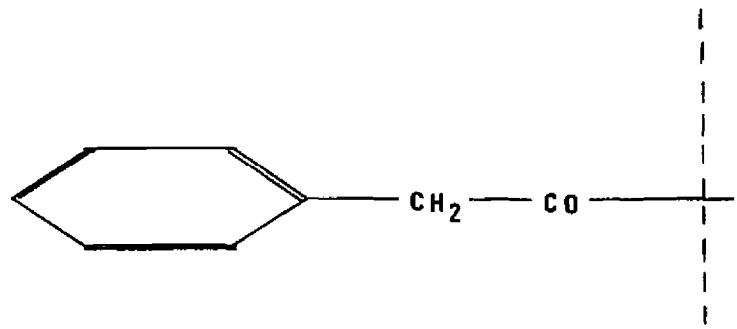
(The vertical dotted line to the left of the nucleus is added by me to facilitate the explanation of different penicillins.)

Penicillins differ according to the kind of chemical group(s) attached or coupled to this common nucleus to the left of the vertical dotted line. The attached or coupled group is called a "side-chain". Reference is first made hereunder to the relevant natural penicillins derived from culturing moulds through fermentation.

(13). Penicillin G. This natural penicillin is also known as "benzyl penicillin" because of the presence of the benzyl group (see paragraph (4)(ii) above) in the side-chain. This side-chain is attached by being substituted for one of the hydrogen atoms, H,

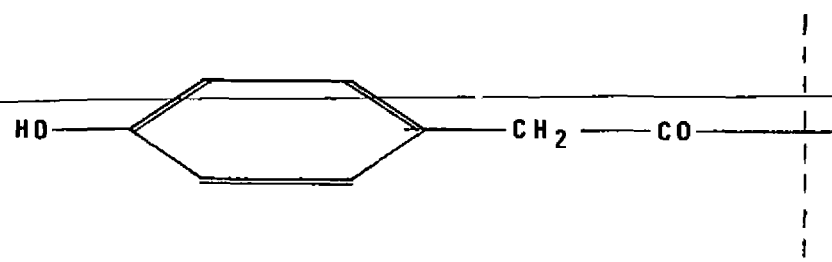
in .... /23

in the amino group, NH_2, in the nucleus. The formula of the side-chain is -



This was the best known and most widely used penicillin until the advent of modern semi-synthetic penicillins. It was, however, not acid stable. Hence administration was by injection rather than by mouth. It was mainly active against a large number of Gram-positive bacteria but not very active against the Gram-negative kind.

(14). Penicillin X. A natural penicillin, also known as para-hydroxybenzyl, with the formula of its side-chain as follows -

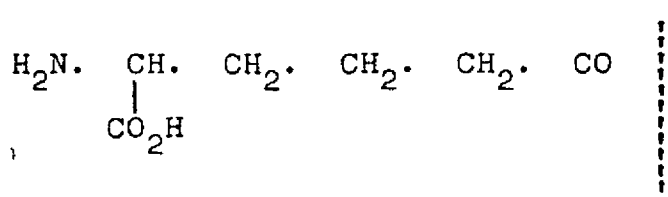


It will be observed that, differing from Penicillin G, it has an hydroxy group attached to the phenyl ring in the para-position.

This .... /24

This penicillin was isolated and named by Bristol. It was widely known before 1962. Its properties were similar to those of Penicillin G, e.g., it was active against Gram-positive but not acid stable or very active against Gram-negative bacteria. It was relatively difficult to produce and was never used or commercially marketed.

(15). Penicillin N. Also a natural, previously known penicillin. It contains the nucleus 6 -APA with an unusual side-chain of which the amino radical H_2N forms part -



It is not acid stable and consequently unsuitable for oral use. But, contrary to other natural penicillins, it is active against Gram-negative bacteria. As already mentioned Beecham used it as

a .... /25

a lead compound for evolving the discoveries for the 1959 and 1963 Patents.

(16). Semi-synthetic penicillins. Those made partly by using the natural nucleus, 6 -APA, and for the rest by synthesizing therewith some appropriate acid in the side-chain. In the 1959 Patent, for example, amino-acyl substituent groups were introduced into the amino group of the nucleus, NH_2, by replacing one of the hydrogen atoms, H.

(17). Asymmetric carbon atom and the epimers. In the formula of alpha-amino-phenylacetic acid in paragraph (6) above, the carbon atom, C, in the centre of the formula, has four different groups attached to it - a phenyl group (the hexagonal symbol), a hydrogen atom, H, an amino group, NH_2, and a carboxylic acid group, COOH. Hence, the central carbon atom so attached is not

symmetrical .... /26

symmetrical. Chemists say it is an "asymmetrical carbon atom". The resultant compound exists in a "right-handed" and a "left-handed" form or epimer. Each is the mirror image of the other. The two forms are known respectively as the D -epimer (for dextro or right) and the L -epimer (for laevo or left). Most penicillins have an asymmetrical carbon atom and therefore exist in the D and L epimeric forms. Ordinarily when the compound is made, a mixture of the two epimers is obtained - a DL or D + L or "racemic" mixture. There was some dispute on the evidence about whether the mixture is itself a chemical compound or merely a physical mixture. That dispute need not be resolved. It is, however, quite feasible, although relatively more difficult, to prepare a compound consisting exclusively of the one or other epimer, the D or the L, as the case may be, each having different degrees of

activity .... /27

activity against bacteria.

(19). Hydroxy substituted penicillins. These are the alpha-aminophenylacetamido penicillins of the 1963 Patent. The hydroxy group is attached to the phenyl ring in the para, meta, or ortho position. The general formula for such penicillins appears in that Patent - see below. They are also known as the alpha-amino-benzyl penicillins, presumably because the benzyl ring is also involved in their structure - see paragraph (4)(ii) above.

(20). The expert witnesses. Professor Rinehart and Dr Menotti testified for Bristol and Dr Nayler for Beecham. All are highly qualified, experienced, and skilled chemists. Professor Rinehart has specialized in antibiotics on the academic side as professor of chemistry at the Illinois University. He admitted that he was not a penicillin chemist - he had never

"worked .... /28

"worked in the penicillin area". Dr Menotti joined Bristol in 1943. In 1958 he took overall charge of its research activities as a Vice-President and Scientific Director. He is familiar with the research and industrial production of penicillin, but said that since the 1950s his work has been largely administrative rather than research, although he has supervised the latter. Dr Nayler has been with Beecham since 1948. He is now its senior organic chemist and is an Associate Scientific Director. He has supervised its research of penicillin drugs since 1956. He was concerned in the isolation of the penicillin nucleus, 6 -APA, and was co-inventor in respect of the 1959 and 1963 Patents. He is the author of several publications. The learned Commissioner and the Court a quo preferred the evidence of Dr Nayler to that of Professor Rinehart and Dr Menotti wherever it differed. That

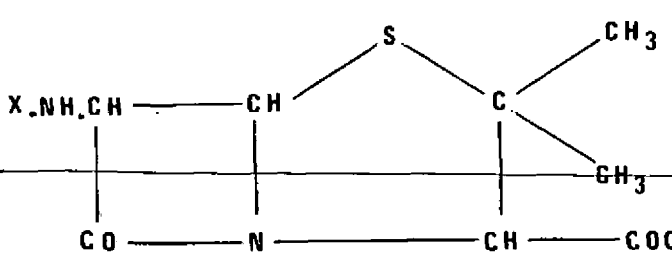
approach..... /29

approach was not seriously challenged before us.

THE 1959 PATENT

This patent was registered in Beecham's favour for penicillins derived from the nucleus, 6 -APA, according to a general formula. It will be recalled that the nucleus contains the amino group, NH_2 - see paragraph (12) of the Glossary. The consistory clause of the specification states -

> "It has now been found according to the present invention that new penicillin derivatives having valuable antibiotic activity can be obtained by introducing aminoacyl substituent groups into the amino group of (the nucleus, 6 -APA). Accordingly, the present invention provides new penicillin derivatives of the general formula:



> where X is an amino substituted acyl group containing ...."

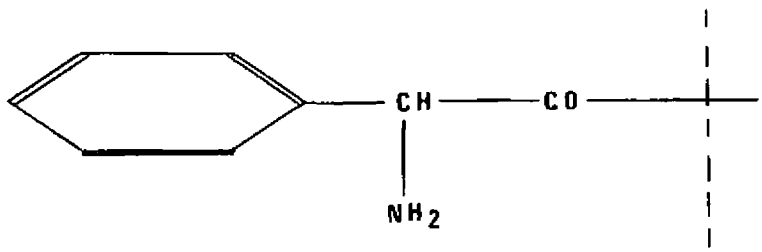
The .... /30

The products of this general formula are claimed in Claim 1.

It will be observed that the X group (the side-chain) is attached by being substituted for one of the H atoms in the amino group, NH_2, in the nucleus. What X can consist of is described in some detail in the specification. A list of five different substituent categories are given as examples of X in the formula. Example (ii) thereof was much canvassed in evidence. But its details are no longer relevant. It suffices merely to say that the expressed preferred class of this Example's compounds did not include any with the hydroxy substituent attached to the phenyl ring - that was common cause; and that it included the compound α-aminobenzylpenicillin. (See paragraph (7) of the Glossary.)

This last-mentioned penicillin forms the subject matter of Example 11 (eleven) in the specification and of Claim 8. This compound,

AB 1060, was made and tested by Beecham in November 1958. The formula of its side-chain attached to the nucleus is -



It will be noticed that the phenyl ring is naked - it is without any substituent group. But the amino group, NH_2, is attached by substitution for one of the H atoms on the benzyl ring. The first carbon atom being asymmetrical, AB 1060 was a DL mixture. In January 1960 Beecham made and tested the D epimer compound thereof, AB 1341, and in August 1961, the L epimer compound, AB 1394. Both have the same formula mentioned above. The former, AB 1341, was successfully marketed from July 1961 under the trade name "ampicillin". It was the best of the penicillins produced at that time, being active against both Gram-positive

and .... /32

and Gram-negative bacteria, and was separately patented.

According to the consistory clause the new penicillin derivatives have "valuable antibiotic activity". A further paragraph in the body of the specification (which I shall call "the promissory clause") expanded on the promise of their value in these terms (my lettering to facilitate reference):

> "The compounds of the present invention are of value (a) as antibacterial agents, (b) as nutritional supplements in animal feeds, (c) as agents for the treatment of mastitis in cattle and (d) as therapeutic agents in poultry and animals, including man, in the treatment especially of infectious diseases caused by (e) Gram-positive and (f) Gram-negative bacteria."

It is necessary and important to construe this promissory clause for it was repeated in the 1963 Patent. Bristol contended that this clause promised that every compound of the invention would possess all of the properties mentioned in (a)

to .... /33

to (f). That construction is unacceptable. The invention, as described and claimed in the specification, covers several hundreds of thousands of compounds. That was common cause. Hence it would be quite unrealistic to construe the clause as if it had read "the compounds of the present invention are each of value in every one of the respects in (a) to (f)". See Smith Kline & French Laboratories' Application (1968) R.P.C. 88 at p. 90, l. 37-46. Any ordinary reader of the specification, having the necessary skill in the art of penicillin chemistry, would not understand the clause to convey such a comprehensive, extravagant promise for the compounds. In the context of the specification and in the absence of any words implying such comprehensiveness, he would understand it to mean merely that the compounds are all of value in one or more but not necessarily all of the respects

mentioned ..../34

mentioned in (a) to (f), and in particular, that not necessarily all or any particular one or group of those compounds have value as a therapeutic agent in treating man for infectious diseases caused by Gram-negative bacteria. Thus, in regard to the latter aspect, of the 19 examples of various compounds of the invention detailed elaborately in the body of the specification, 16 are stated to inhibit "Staph. aureus" (in example 14, "Staph.oxford") at specified levels in in vitro tests. Those are all Gram-positive bacteria. There is no mention in the examples of any inhibition of Gram-negative bacteria. BUCKLEY, L.J., with BROWNE, L.J. concurring, construed a similar promissory clause in substantially the same way in the as yet unreported case decided in the English Court of Appeals of Beecham Group Ltd's Patent Application, on 19 July 1979. That is, I think, the correct

interpretation .... /35

interpretation of the 1959 clause. True, it is tantamount to construing the respects mentioned in (a) to (f) to some extent disjunctively rather than wholly conjunctively, despite the use of "and" therein, but that is warranted in the context and circumstances already mentioned (cf. Barlin v. Licensing Court for the Cape 1924 A.D. 472 at p. 478). Bristol contended that the reader of the specification would then not know, and would have to ascertain for himself, which value(s) a particular compound of the invention had. That may be so, but that cannot affect its true interpretation.

THE 1963 PATENT

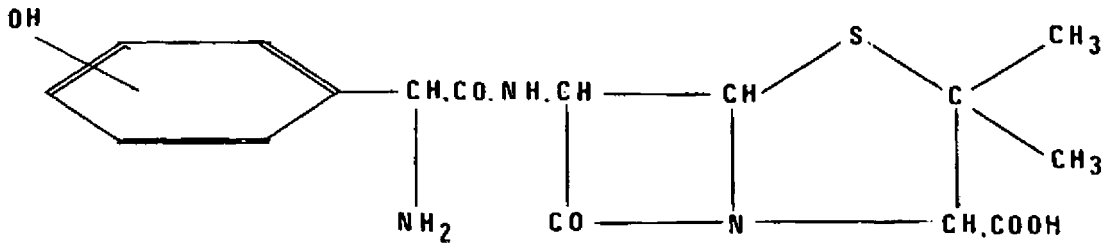
The alleged invention relates to "new penicillins". The body of the specification starts by referring to and describing the 1959 Patent in these terms -

"we .... /36

"we have described and claimed penicillin derivatives of the general formula .... (of the 1959 Patent supra which is here repeated) .... where X is an amino-substituted acyl group containing .... and having the formula .... (the formula of Example (ii) of the 1959 Patent and some of its constituents are here repeated) .... These compounds are of value as .... (its promissory clause is also repeated verbatim here) .... "

The promissory clause of the 1963 Patent then follows:

"We have now found that certain compounds falling within the general formula .... above have particularly desirable properties especially in respect of their activity against Gram-negative bacteria. Accordingly, the present invention provides new penicillins of the general formula:-



and non-toxic salts thereof."

The products of that formula are the subject matter of Claim 1 - the widest claim. They are the hydroxy substituent penicillins in which the hydroxy group, CH, is attached to the phenyl ring

in .... /37

in the para, meta, or ortho position. The carbon atom, C, in the alpha position is asymmetrical. Hence, a product of the formula can be a D + L mixture, or a D or L epimeric form thereof.

Indeed the body of the specification says:

> "The compounds of the present invention contains an asymmetric carbon atom in the side-chain and thus can exist in two .... forms. It is understood that the present invention includes both epimeric forms as well as the dl - mixture."

That means Claim 1 covers 9 products - a D, L, and D + L product for the para and each of the meta, and ortho positions, or if the D + L mixture is not regarded as a true product (cf. par. (17) of the Glossary), only 6 products. Indeed, Claim 2 is limited to those 2 or 3 products, as the case may be, in which the hydroxy substituent is in the para - position. It reads:

> "2. 6 - (p - Hydroxy - α - aminophenylacetamido) - penicillanic acid and non-toxic salts thereof."

The .... /38

The D -epimer product of this Claim, made by Beecham in 1964 (AB 2333), became the highly successful penicillin, amoxycillin, to which these infringement proceedings relate. Claim 3 is limited to those 2 or 3 products in which the hydroxy substituent is in the meta - position. It reads:

"3. 6 - (m - Hydroxy - α - aminophenylacetamido) - penicillanic acid and non-toxic salts thereof."

No specific claim is made for products in which the hydroxy substituent is in the ortho - position, but they, like those of Claims 2 and 3 too, are covered by the broad, general Claim 1. There are, therefore, at most 9 different products covered by the 1963 Patent. They are also known as the alpha - aminobenzyl penicillins - see paragraph (19) of the Glossary.

Claims 4 to 12 are process claims, and Claim 13 a product-by-process claim. Nothing turns on them in these proceedings .... /39

proceedings.

At various times Beecham made and tested the compounds corresponding to those claimed products and some of those of the 1959 Patent. The tests were both in vitro and in vivo. The results had to be disclosed for the purpose of this litigation. Bristol relied heavily on them to prove (the onus being on it) that Beecham's alleged invention was not useful or inventive. These results will be tabulated presently.

In order to consider and decide those two issues our first task is to ascertain the nature of the alleged invention of the 1963 Patent and its promised usefulness according to the proper construction of its specification (Gentiruco A.G. v. Firestone S.A. (Pty.) Ltd. 1972 (1) S.A. 589 (A) at pp. 609 H and 613 F - H). For these purposes it is permissible to have

regard .... /40

regard also to the specification of the 1959 Patent, since it is incorporated into the 1963 Patent specification, expressly as to part thereof and by reference as to the remainder. The manifested intention of the patentee was that the two specifications should be read together for those purposes (cf., for example, Wessels, Law of Contract, 2nd ed., vol. 1, par. 1979). Now the 1959 Patent covers multifarious compounds, some hundreds of thousands of them. According to its promissory clause, which has already been construed above, not necessarily all or any particular one of those compounds have value as a therapeutic agent in treating man for infectious diseases caused by Gram-negative bacteria. That clause is repeated in the specification of the 1963 Patent, obviously with the same meaning. The consistory clause of the latter then describes its alleged

invention .... /41

invention as being the discovery that, within the multifarious compounds covered by the 1959 Patent, there is a small group of at most 9 compounds, namely, the alpha - aminobenzyl penicillins with hydroxy substituents on the phenyl ring, each of which has (according to its promissory clause) -

> "particularly desirable properties especially in respect of their activity against Gram-negative bacteria."

The precise meaning of that clause in its above context was much debated before us and in the Courts below. The argument was limited to the property in respect of activity against Gram-negative bacteria in man. Counsel for Bristol contended that -

(i) the 1959 Patent promised that all of its compounds had some such activity;

(ii) .... /42

(ii) that the 1963 Patent, by repeating that promissory clause and following it up with its own, abovequoted promissory clause, was in effect making a comparison and asserting that its products surpassed those of the 1959 Patent in such activity;

(iii) that that was understood too by the use of the adverbs "particularly" and "especially", which connoted an exceptional, excellent, or unusual superiority or degree in activity; and

(iv) that, in particular, the 1963 Patent promised that all its products were even better in such activity than ampicillin, the best penicillin of the 1959 Patent.

In support of that argument, especially the last submission in (iv), counsel referred to a certain table of results also

incorporated .... /43

incorporated in the 1963-Patent specification. The expressed purpose of its incorporation was to "illustrate" the activity in vivo of two of the compounds of the invention compared to ampicillin (AB 1341) when tested orally and subcutaneously in mice against two kinds of Gram-negative bacteria, Salm. TM. and Kleb. Pneu. The two compounds of the invention were those claimed in Claims 2 and 3 of the Patent (AB 1886 and AB 1951). The results of the tests showed that the latter compounds had better activity than ampicillin.

For reasons that follow that argument cannot prevail.

As to the submission in (i), that has already been disposed of against Bristol in dealing with the 1959 Patent. Its promissory clause did not assert that all or any particular

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one or group of its multifarious compounds were active against Gram-negative bacteria. As to (ii), (iii), and (iv), the only relevant comparison impliedly made in the 1963 Patent is that all of its newly discovered nine products have inter alia that particular property, which is not the case with the products of the 1959 Patent. That the promissory clause of the 1963 Patent does not use any comparative adjective to qualify "properties" is against Bristol's submissions. If such a comparison were intended some expression such as "particularly better properties" would surely have been used. Indeed, it is unlikely that the patentee could have intended any such comparison having regard to the vast number of untested products of the 1959 Patent whose actual properties must have been unknown. But be that as it may, the adjective used is "desirable", i.e., worth wanting or wishing

for .../45

1963 products with ampicillin in respect of Gram-negative activity. But the comparison is a specific, limited one, confined to those two products and those tests. The purpose of including it in the specification was merely to illustrate "the particularly desirable properties" in such respect possessed by those two products. Besides, the promissory clause does not assert that the 1963 products are all equally active in that respect. Hence, the inference cannot be drawn from the inclusion of the table that, firstly, a general comparison between the 1963 products and ampicillin was intended and was to be made, and secondly, that the 1963 Patent promised that all the other products were also better in the respect mentioned than ampicillin. Bristol also relied on the evidence of Dr Nayler who, referring to the table, said that at the effective date of the 1963 Patent, i.e., 2 November

1962 .... /47

1962, ampicillin had become an outstanding penicillin and the standard against which future penicillins should be measured. But that evidence referred to the commercial utility of future penicillins and not to the meaning of the specification of the 1963 Patent. Indeed, if it did refer to the latter, it was inadmissible, since it is for the Court and not an expert witness to say what it means (see the Gentiruco case, 1972 (1) at pp. 614 G, 616 D - 618 E).

To sum up. According to the consistory and promissory clauses of the 1963 Patent the alleged invention is the discovery or isolation from the multifarious compounds of the 1959 Patent of a small group of at most 9 alpha-aminobenzyl penicillins with hydroxy substituents on the phenyl ring. Each of those penicillins has the desirable property inter alia of being

active .... /48

active against Gram-negative bacteria in man to some extent but not necessarily to an equal extent. It does not assert that all or any of them possess that property to a greater extent than the compounds of the 1959 Patent or any particular one of them like ampicillin, save perhaps to the limited extent reflected by the abovementioned illustrative table in the specification.

The Court a quo reached substantially the same conclusion. On the other hand the learned Commissioner adopted a somewhat different approach. He appears to have assumed rather than decided in Bristol's favour that the 1963 promise did import a comparison in activity against Gram-negative bacteria between the compounds of the respective Patents. He however held that the only relevant comparison would be, not merely with a limited number of compounds of the 1959 Patent like

ampicillin .... /49

ampicillin, but with the hundreds of thousands of its compounds not selected in the 1963 Patent. I shall advert to that approach in due course when dealing with the issue of utility.

THE ISSUE OF INUTILITY

According to section 1(vi) of the Act an "invention" must inter alia be a "useful" composition of matter. If it is not, the patent covering it can be invalidated for non-usefulness, i.e., inutility - section 23(1)(e) read with sections 43(1) and 53(a) and (b). The meaning of "useful" in that context was canvassed at the Bar. The relevant part of the definition of "invention" reads (my italics):

> "any useful composition of matter capable of being used or applied in trade or industry."

According to section 23(1)(c) one of the grounds of invalidation is that

"the .... /50

"the invention does not relate to .... composition of matter .... which is capable of being applied in trade or industry."

The other ground in section 23(1)(e) is that "the invention is not useful". The query raised by us was whether "useful" there meant "capable of being used in trade or industry", since "used" in relation to trade or industry was omitted from the ground in section 23(1)(c). On further reflection after argument I do not think that it does mean that. The definition of "invention" embodies two different elements, "useful" and "capable of being used or applied in trade or industry". They are then reflected respectively in subparagraphs (e) and (c) of section 23(1) as different, separate grounds of invalidation, except that in sub-paragraph (c) "used" was omitted, possibly inadvertently. Moreover, "useful" bears, not its ordinary meaning, but, "the

specialised .... /51

specialised meaning", well-known in patent law here and elsewhere, of "effective to produce the result aimed at" by the invention (Frank and Hirsch (Pty.) Ltd. v. Rodi and Wienenberger Aktiengesellschaft 1960 (3) S.A. 747 (A) at p. 755 C - D; the Gentiruco case, supra, at p. 609 G - H). Thus, provided the alleged invention is effective to produce the result aimed at or promised, it is "useful", even if that result is not a commercial or pecuniary success and is, indeed, only of very small use, advantage, or value (BLANCO WHITE, Patents for Inventions, 4th ed., p. 183; The Badische Anilin and Soda Fabrik v. Levinstein (1887) 4 R.P.C. 449 at pp. 462, l. 38, and 466, l. 34 (HL); and Valenski and Another v. British Radio Corporation Ltd. (1973) R.P.C. 337 (CA) at p. 378, l. 1), unless the specification, expressly or impliedly, promises otherwise. (See BLANCO WHITE, ibid). Consequently,

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I do not think that the Act, by introducing as a requirement of an "invention", that it must be "capable of being used or applied in trade or industry" intended thereby to alter that well-established and well-known connotation of "useful". Possibly, if an invention were commercially unsuccessful, it might also be regarded as being incapable of being used in trade or industry, which would afford under our Act another ground for invalidating the patent that is separate and different from that of non-usefulness. But no view need be expressed thereon for that ground was not pleaded.

Usually it is unnecessary for a specification to contain any express promise of the result to be achieved by the invention, except perhaps in chemical patents, especially those of selection cases, "where the inventiveness lies in the

discovery .... /53

discovery that a particular compound has valuable properties"

(see BLANCO WHITE, supra, at pp. 46, n. 19 and 209 n. 27). Where a particular result is expressly or impliedly promised, it must be achievable by the invention, otherwise the patent can be invalidated for inutility (BLANCO WHITE p. 181). Here the result aimed at or promised by the 1963 Patent is set out in the specification and has already been construed. It is that (in so far as it is relevant here) each of its products will have the property of being active against Gram-negative bacteria in man. No promise is made of the degree of that activity or that any such product will necessarily be commercially successful.

Bristol relied on the MIC results of the in vitro tests and the CD_{50} results of the in vivo tests conducted by Beecham in order to prove (the onus being on it) the alleged

inutility .... /54

inutility of some of the 1963 penicillins in regard to their activity against Gram-negative bacteria in man. The most convenient way to reflect the results of the tests of the 9 compounds of the 1963 Patent is in a schedule attached to this judgment. The Glossary explains the terms, abbreviations, and figures used therein. It will be recalled that the lower the test figure, the higher the efficacy of the compound. When the symbol > is used in relation to a figure it means "greater than" but how much greater is unknown; conversely, the symbol < means "less than" but how much less is unknown. In the course of a programme of research designed to find the most effective penicillins Beecham had also tested some diverse compounds of the 1959 Patent, about 30 for MICs, and of those about 20 also for CD_{50}s. Two of the best and three of the worst results are

also ..../55

also given in the schedule for comparison or illustration. Between those extremes the other 1959 compounds so tested exhibited anti Gram-negative activity in varying degrees.

The results of the tests and the evidence showed that those of the 1963 compounds, AB 1886, 1951, 2205, and 2333, were in some respects better than or at least comparable to those of ampicillin and some of the other 1959 compounds. Indeed, AB 2333 (amoxycillin) turned out to be a most successful penicillin and superior to ampicillin.

Bristol maintained, however, that the results of the tests on compounds AB 1953, 2204, 2374, 20088, and 20089 of the 1963 Patent were so poor that they showed inutility which invalidated the whole patent. I think that the results relating to AB 20088 and AB 20089 can be disregarded. (Only

the .... /56

the MICs were available since no *in vivo* tests were done thereon.)

Professor Rinehart did not regard them as comparable with the other data since these compounds were only tested in 1976, at least 12 years after the tests of the other compounds, during which time the relevant conditions, for example, the test organisms, may have changed. The other experts did not gainsay him on that point. True, Professor Rinehart and Dr Menotti inferred that Beecham itself had rated those two compounds (AB 20088 and 20089) very poorly since it did not test them *in vitro* originally or *in vivo* at all. But according to Dr Nayler the true reason for that was that better compounds were available at the time for testing.

As to the other compounds, AB 1953, 2204, and 2374, their results were not as good as those of the other 1963

compounds .... /57

compounds. The effect of the opinions expressed by Professor Rinehart and Dr Menotti was that their results were so poor or weak that the compounds must be regarded as being practically useless against Gram-negative bacteria in man. Dr Nayler, while expressing a more optimistic view, conceded that some of the results showed poor activity in that respect. Their views, however, were influenced, at least to some appreciable extent, by commercial considerations and by a comparison of those results with those of the better compounds of the 1959 Patent, like ampicillin. The utility of the compounds is, however, not to be measured in that way. For the specification of the 1963 Patent merely promises that its compounds would each be active against Gram-negative bacteria in man, not that they would be equally active inter se, or more active in that respect than ampicillin

or .... /58

or any other penicillin of the 1959 Patent, or that they would be commercially successful. Furthermore, it was common cause between all the experts that, according to the tests' results, all the compounds in question exhibited that they did have such activity. Hence, on that simple approach, Bristol did not prove that those compounds were inutile.

However, Bristol set such great store by the results of Beecham's tests on the compounds that, I think, their probative value on the issue of utility should be dealt with.

The expert witnesses, especially Drs Menotti and Nayler, explained that the *in vitro* and *in vivo* tests are not final for establishing the compounds' efficacy against Gram-negative bacteria in man. True, they do give some indication of such efficacy: hence the inclusion of the aforementioned

illustrative .... /59

illustrative table in the specification of the 1963 Patent of the CD_{50} results of its compounds AB 1886 and 1951 and of AB 1341 (ampicillin) for that purpose. But actually such tests are merely preliminary or screening tests done in order to determine whether or not to proceed further with the investigation by conducting other tests for the purpose of trying to establish such efficacy. As further investigation and testing require the expenditure of time, energy, and money, it is usually only pursued in respect of those compounds with more promising initial results. That does not necessarily mean, however, that those with less promising results would not be efficacious in the treatment of bacteria in man. To be sure of that one would still have to do further intensive tests, even on humans. As counsel for Beecham pointed out, the compound AB 2333 (amoxycillin) affords a

striking .... /60

striking example of that: the earlier tests on it did not suggest that it would be substantially more efficacious than ampicillin; indeed, the further investigation of its properties was originally given "a low priority"; and it was only 4 years later (1968) that tests in man revealed its high efficacy because of a greatly superior absorption into the blood. And incidentally, the evidence of Dr Nayler thereanent indicated that those tests involved doing extensive, laborious toxicity tests on a large group of animals - a major undertaking which would not be lightly undertaken. Of course, the more tests that are done and the more results that are available, the more cogent the inference that can be drawn or the more confident the opinion that can be expressed. Professor Rinehart admitted as much in this passage:

"I presume as a general proposition, the more results

you .... /61

you get, the more .... confident you can be in the opinion that you expressed? .... I have that general feeling."

Dr Nayler said:

> "Well clearly the more tests one does the more accurate an estimate one can arrive at as to the merits of the compound."

and Dr Menotti:

> "well, as we said, this (i.e. the MIC) is a screening test, and if you want to do accurate work, you have to select the compound and go ahead and do a more extensive testing".

Now in regard to the compounds in question, AB 1953, 2204, and 2374, it appears that only the one series of preliminary, screening tests was done on them by Beecham. Bristol, on whom the onus rested, adduced no evidence of any tests that it might have done on those compounds to substantiate its allegations of inutility. In all those circumstances I do not think that one can infer from those tests' results alone that the compounds in

question .... /62

question were insufficiently active against Gram-negative bacteria in man to show the alleged inutility.

In coming to that conclusion I have not overlooked this particular aspect concerning the compound AB 2374, the L -epimer of amoxycillin. In its particulars of inutility Bristol alleged:

> "Claims 1 and 2 include matter which lacks utility, because the L -epimer of Amoxycillin is useless as an oral penicillin."

Beecham had in fact previously admitted that it was useless as such. But that did not mean that it was useless for aministration in man by subcutaneous injection. Dr Nayler explained that, while oral administration of penicillin is more convenient and popular, subcutaneous administration is still done and in some

cases .... /63

cases is necessary or preferred. Bristol submitted, however, that the specification of the 1963 Patent promised that each of its compounds would be efficacious against Gram-negative bacteria in man when administered both orally and subcutaneously. That is untenable - the promissory clause does not mention the method of administration at all. At the final stage of the proceedings before the learned Commissioner Bristol applied to amend its above allegation by deleting therefrom "as an oral penicillin", so as to be able to rely on an alleged general uselessness of the compound, i.e., even when administered subcutaneously. The amendment at that belated stage was refused. The Court a quo declined to interfere with that exercise of the learned Commissioner's discretion, and were it necessary, we should, I think adopt the same attitude. But in fact the amendment would not

further .... /64

further Bristol's case, for it did not prove, for reasons already given, that the compound was generally useless.

Lastly, on the issue of inutility, I revert to the learned Commissioner's approach. A further allegation of inutility by Bristol was that -

> "the ortho-hydroxy and meta-hydroxy forms of the penicillin derivative which are selected from the compounds of (the 1959 Patent) have no advantage against Gram-negative bacteria above that of unselected compounds. For this reason Claims 1 and 3 include matter which lacks utility."

Bristol was asked for the purposes of the trial what those "unselected compounds" were. It replied: "The unselected compounds will include Ampicillin". Now the learned Commissioner assumed (rather than decided) in Bristol's favour that the promissory clause of the 1963 Patent meant that its compounds were to be

compared .... /65

compared with those of the 1959 Patent in respect of their activity against Gram-negative bacteria. Having regard to that promise and Bristol's particulars of inutility he held that it could not prove its case by comparing the compounds of the 1963 Patent merely with ampicillin or the other comparatively few tested compounds of the 1959 Patent; the only relevant comparison would be with the hundreds of thousands of compounds of the 1959 Patent not selected for the 1963 Patent; and as that comparison had not been made, Bristol failed to prove the alleged inutility.

Before us Bristol did not attack that approach. It maintained, however, that it was quite unrealistic and wrong to require of Bristol that it should have to perform the allegedly impossible task of comparing the 1963 compounds with all the unselected multifarious compounds of the 1959 Patent in order to

prove .... /66

prove the alleged inutility. But there was no evidence that that was impossible. Possibly some compounds that were proved to be representative of the unselected 1959 compounds in respect of anti-Gram-negative activity could have been tested and their results accepted for the purpose of such comparison. That that might have entailed extensive or numerous tests is of no moment, for as Beecham rightly submitted, there is no reason why it should be easy, or be made easy, to prove inutility. Indeed, Bristol actually relied on the few tested compounds of the 1959 Patent as being representative of the mass of its other compounds. That they were so representative was sought to be substantiated by mere inference and not by direct evidence. This judgment would be unduly prolonged if this matter were to be elaborately canvassed. It suffices to say only this. The passages in

the .... /67

the evidence of Dr Nayler that were referred to do not, in my view, support that inference, let alone prove that the other 1959 compounds would have similar activity against Gram-negative bacteria as the tested compounds. Moreover, these aspects should not have been left to mere inference - they should have been canvassed directly with the expert witnesses. Also untenable is Bristol's submission that that was not done because of certain particulars furnished by Beecham for trial purposes, and that, in any event, those particulars precluded Beecham from contesting such representativeness. For in those particulars Beecham did not admit or assert that the tested compounds or the results of the tests were representative in the sense contended for. Indeed, as counsel for Beecham rightly submitted, the tested compounds of the 1959 compounds were selected for being ...

/ 68

being made and tested, not because they were representative of the other compounds in respect of their activity against Gram-negative bacteria, but in the ordinary course of a programme of research designed to find the most effective penicillins. At most, they were merely representative in the chemical sense. As Dr Nayler said:

> "you try to make compounds which are relatively simple to make but also representative in the chemical sense."

Furthermore, it cannot be inferred merely from the specification of the 1959 Patent alone that those of its compounds that had so far been tested were representative of all its compounds in respect of activity against Gram-negative bacteria.. On the contrary, according to the 19 Examples of its compounds given therein to illustrate the invention, 16 exhibited activity against

Gram-positive .... /69

Gram-positive bacteria, but none were stated to have been tested for Gram-negative bacteria. And its promissory clause, in so far as it might have been based on the tested compounds, did not assert or predict that all of its compounds would, in consequence of those tests, be active against Gram-negative bacteria.

So, in my view, Bristol failed to prove that the tested compounds of the 1959 Patent were representative of the others in respect of activity against Gram-negative bacteria. It follows that even on the learned Commissioner's approach, Bristol failed to prove the alleged inutility.

The appeal in respect of the issue of inutility must therefore fail.

THE ISSUE OF INVENTIVENESS

This inquiry is whether or not the alleged

invention .... /70

invention of the 1963 Patent was, according to section 23(1)(d) of the Act -

> "obvious in that it involves no inventive step having regard to what was common knowledge in the art at the effective date."

That inquiry is threefold - (a) what was common knowledge in the art at the effective date, i.e., 2 November 1962; (b) whether the invention involved any further step in relation to such common knowledge (usually and conveniently referred to as "a step forward"); and (c) whether that step was inventive, i.e., not obvious (cf. the Gentiruco case, supra, 1972 (1), at p. 653 G - H).

The art concerned was the chemistry of penicillins, an important part of the chemistry of antibiotics in which the pharmaceutical industry and universities are greatly interested. The pharmaceutical industry is international and

highly .... /71

highly competitive. According to Dr Menotti there are in the U.S.A. alone possibly 30 large pharmaceutical organisations with about 4000 chemists. Presumably many of the industrial and academic chemists would be engaged in the chemistry of penicillins because of their importance nowadays as antibiotics. According to the Gentiruco case, supra, 1972 (1) at p. 654 A, common knowledge is the knowledge of the art or science appertaining to the invention that, at the effective date of the patent, was common to most of the ordinary skilled or qualified persons engaged in that art or science. Such common knowledge is fundamental to the whole inquiry, for it is the standard by which one determines whether any step forward has been achieved (see, for example, Veasey v. Denver Rock Drill and Machinery Co. Ltd. 1930 A.D. at p. 282), and, if so, whether the step was obvious to

any .... /72

any of those possessing that knowledge (the Gentiruco case, pp. 655 B - D; 660 H). For the purpose of determining those matters the Courts below adopted the well-known approach of ascertaining who would be the notional "person skilled in the relevant art or science" or (the same exercise) the hypothetical "addressee" of the specification of the 1959 and 1963 Patents. Although I prefer the approach in the Gentiruco case, the result of both approaches is substantially the same, since the "addressee" or "person skilled in the art" would in effect be the typical representative of "the ordinary skilled or qualified persons engaged in the art."

The question arose and was canvassed before us and in the lower Courts whether "the ordinary skilled or qualified persons engaged in the art" should be research chemists,

i.e. .../73-

i.e., those concerned merely with the discovery, making, and testing of new penicillins, or industrial chemists, i.e., those concerned with the manufacture, production and marketing of such penicillins. The learned Commissioner held that it was not the research chemists but presumably some other competent persons engaged in the practical manufacture thereof. He held that neither Professor Rinehart nor Dr Menotti was shown to be skilled in the latter field and thus qualified to testify about what was common knowledge at the relevant time and on other aspects of the issue of inventiveness, and that consequently "the essential foundation" of Bristol's case on this issue was "missing". The Court a quo did not think it was necessary to distinguish between the two categories because, it said, those who are engaged in manufacture will probably also be skilled chemists. Regard

should .... /74

correctly in my view, that where these witnesses differed, the testimony of Dr Nayler was to be preferred.

Common Knowledge

Apart from the ordinary, general knowledge of the relevant principles of the chemistry involved such as, for example, the use of lead compounds and the making of simple substitutions in preparing new compounds, the following facts or information, it was accepted, were common knowledge as at 2 November 1962:

(a) The existence of the better-known natural penicillins including Penicillins G, X, and N. The structures, properties, and use of Penicillins G and X (see paragraphs (13) and (14) of the Glossary) must also have been commonly known. But it was not proved that the structure and properties of Penicillin N (see paragraph (15) of the Glossary) were common knowledge.

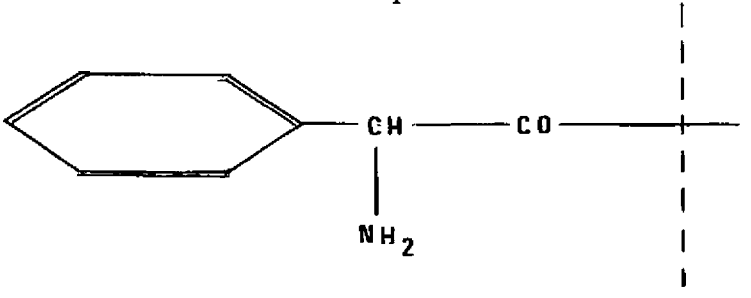
(b) The discovery or isolation of the nucleus of the penicillin molecule and its structure, 6 -APA, which meant that many new penicillins could now be synthesized by

coupling .... /76

coupling some other appropriate side-chains to it. See paragraphs (12) and (16) of the Glossary

(c) Broadly, the granting of the 1959 Patent for a massive class of semi-synthetic amino-acyl penicillins of a general formula using the 6 -APA nucleus, which penicillins all have some value as anti-bacterial agents.

(d) Ampicillin, as one of the products of the 1959 Patent, its chemical structure, its good activity against both Gram-negative and Gram-positive bacteria, and its success commercially and otherwise. It is dealt with in the description above of the 1959 Patent. It was the L epimer of the compound AB 1341. For easy reference its structural formula of the side-chain attached to the 6 -APA nucleus is repeated here:



As to (c), the precise extent to which the contents of the 1959 Patent were common knowledge was disputed. Bristol maintained that its entire contents became common knowledge, or at least its "basic teaching". Because the pharmaceutical industry is so highly competitive and the universities

are .... /77

are so interested in modern antibiotics, it is very probable (and indeed the experts said) that penicillin chemists would undoubtedly have been interested in and did read the 1959 Patent when it was published. But that does not per se render any particular part of its contents common knowledge in the sense contemplated by the Gentiruco case, 1972 (1) at pp. 655 D, 656 D - H. However, I shall assume, without deciding, in Bristol's favour that the relevant contents of the 1959 Patent did become common knowledge as at 2 November 1962.

Bristol also submitted that it was part of the common knowledge as at 2 November 1962 that all the penicillins of the 1959 Patent were also active against Gram-negative bacteria. But no evidence was adduced to prove that. The promissory clause in its specification was relied on, but that

merely .... /78

merely asserted that some, not necessarily all or any particular one, of its products had such activity.

The following matters, it is important to note, nad not become common knowledge by 2 November 1962 -

(i) The nine compounds of the 1963 Patent that Beecham, and nobody else, had made and tested.

(ii) The MIC and CD_{50} results of those compounds and those few of the 1959 Patent that Beecham had tested for their activity against Gram-negative bacteria.

(iii) The particular nature, structures, and properties of the compounds of the 1963 Patent.

The Step Forward

The alleged invention as claimed in the specification of the 1963 Patent has already been construed.

According .... /79

According to it the step forward was the discovery and isolation, from the vast field of the multifarious compounds of the 1959 Patent, of the small group of penicillins of a particular formula having the hydroxy substituent attached to the phenyl ring, each of which was inter alia active against Gram-negative bacteria in man.

Whether or not that was a step forward on the common knowledge as at the effective date, 2 November 1962, is a question of fact concerning which evidence is admissible (see the Gentiruco case, 1972 (1) at p. 660 D - F). But the question must be investigated and answered in the context of what was commonly known as at that effective date. Facts that only became known thereafter, whether commonly or otherwise, are irrelevant here. I emphasize this because Bristol sought to

rely on the MIC and CD_{50} results of Beecham's tests of the compounds of the 1963 Patent in order to refute the alleged step forward. The argument was that those results showed that at least 4 of those compounds (AB 2204, 2374, 20088, and 20089) and possibly 7 of them (if the DL mixtures are included - AB 1886, 1951, and 1953) were "significantly poorer" than ampicillin in activity against Gram-negative bacteria, and that consequently the embodiments of those compounds in the claims of the 1963 Patent did not represent any step forward, thereby rendering those claims and the whole Patent invalid. That argument is untenable since those results, not being common knowledge as at 2 November 1962, cannot be used for that purpose. They could be used, of course, to prove inutility (and were sought to be so used) or misrepresentation if that had been alleged

(see ..../81

(see section 23(1)(i) of the Act). But they cannot be used here, for the step forward has to be measured and determined by what was common knowledge as at 2 November 1962, and that did not include those results.

Prima facie it would appear that the alleged invention did represent a step forward on the premised common knowledge. For apart from ampicillin (to which I shall refer presently) nothing precise was proved to have been commonly known at the effective date about the mass of compounds of the 1959 Patent or their particular properties; and Beecham's discovery and isolation of the small group of 6 or 9 penicillins from them having inter alia the property of being active against Gram-negative bacteria, does seem to be a distinct advance on such common knowledge, as Beecham submitted. Certainly Bristol did

not .... /82

not prove the contrary. Indeed, the evidence, such as it was, rather supported Beecham's submission in this respect. Dr Nayler said the discovery "represented an advance in the chemotherapy of Gram-negative infections". He was speaking generally of the group there, not, as Bristol contended, with reference to a particular, successful compound of the 1963 Patent. He said as much when he was cross-examined on that statement. And more specifically he said that the group of the three compounds of Claim 2 of the 1963 Patent represented "a useful advance" on the common knowledge of the amino-acyl penicillins. The evidence of Dr Menotti did not gainsay such testimony. Indeed, he in effect conceded it, but with the qualification that some of the 1963 compounds "turned out to be good and some ... no good". That qualification, however, relates to the MIC and CD_{50} results,

which .... /83

which, for reasons already given, are irrelevant here.

For Bristol it was submitted that the commonly known ampicillin of the 1959 Patent was the correct standard by which to measure whether or not the compounds of the 1963 Patent represented a step forward on common knowledge. That submission is unacceptable for reasons that follow. Although all the 1963 Patent's compounds were theoretically covered by the broad general formula of the 1959 Patent, ampicillin differed from the 1963 compounds in that each of the latter had an hydroxy substituent attached to its phenyl ring, whereas ampicillin did not. They were therefore different chemical compounds. It was common knowledge that chemical compounds, even though having closely similar chemical structures or only very small chemical differences, were nevertheless different compounds

which .... /84

which may have entirely different properties. Probably the isolation of ampicillin from among the vast number of the 1959 Patent's compounds, and the discovery that it had activity inter alia against Gram-negative bacteria was itself an appreciable step forward on the common knowledge at the time. Indeed, it was separately patented. It was not proved, however, that in respect of that property ampicillin was representative of all the other compounds of the 1959 Patent, let alone that that fact was common knowledge. By reason of ampicillin alone, therefore, it did not become common knowledge which of all those other 1959 compounds were active against Gram-negative bacteria. Consequently, the isolation therefrom of the small group of the 1963 different compounds also having such activity was by itself, like the discovery of ampicillin, a step forward on common

knowledge .... /85

knowledge as at 2 November 1962. To constitute such a step it was not necessary for those compounds to be better in such activity than ampicillin for it was a different compound. Bristol, however, contended that the alleged invention was then a step sideways and not a step forward, as is required. The short answer to that contention is this. Section 23(1)(d) of the Act only speaks of a "step". That means any real difference, however small, between the alleged invention and common knowledge. Such a difference or step is usually and conveniently referred to as a "step forward". This appears from what STRATFORD, J.A., said in Veasey's case, supra, 1930 A.D. at p. 282:

> "On the issue of subject-matter the difference between the plaintiff's invention and prior common knowledge must be measured and valued. If there is no difference, there is no subject-matter; if there is a difference but it calls

for .... /86

> for no inventive ingenuity to bring it about, there is also no subject-matter; but if there is a real inventive step forward, no matter how small, that is sufficient to give subject-matter to the patent."

For example, if A invents a new chemical compound for the cure of arthritis which is patented and becomes common knowledge, and thereafter B invents a new, different chemical compound also for the cure of that disease, the latter can nevertheless constitute a step forward on such common knowledge. Otherwise it would mean that A's invention would completely close the door to further cures being discovered and patented, which is absurd. That A and B in the present case are the same inventor is of no moment.

The Inventiveness of the Step

The onus was on Bristol to prove that the step forward that Beecham took under the 1963 Patent was not inventive, i.e., that it was obvious and not due to any inventive

ingenuity. A helpful and, in this case, an appropriate test to adopt is whether or not any one of the postulated ordinary skilled or qualified persons engaged in penicillin chemistry, having the common knowledge already premised and being confronted with the inventor's problem as at 2 November 1962, could and would easily himself have taken the step in order to solve the problem (see Veasey's case, supra, 1930 A.D. at pp. 270/1; the Gentiruco case, supra, 1972 (1) at p. 656 E; and Marine Construction and Design Co. v. Hansen's Marine Equipment (Pty.) Ltd. 1972 (2) S.A. 181 (A) at p. 193 A - C). The "ordinary skilled or qualified person" is not, of course, to be regarded as being one of exceptional skill, qualification, or knowledge or as having himself any inventive intuition or ingenuity. According to the specification of the 1963 Patent and Dr Nayler's evidence the

problem .... /88

problem in question was to discover from among the myriad compounds of the 1959 Patent some "new penicillins", as the specification of the 1963 Patent indicates, i.e., other than ampicillin, that were active against Gram-negative bacteria in man. Ampicillin is excluded because it had already been so discovered. The inquiry therefore is whether or not the postulated skilled or qualified penicillin chemist could and would easily have found as at 2 November 1962 that, of the compounds of the 1959 Patents, those 6 or 9 alpha-amino-benzyl penicillins with the hydroxy group attached to the phenyl ring had such activity. The opinions of the expert witnesses on this problem are irrelevant and inadmissible, for it is for the Court to resolve it on the facts, technical and otherwise, that have been adduced in evidence (see the Gentiruco case, 1972 (1) at p. 660 G).

In .... /89

In essence the case for Bristol was this.

The structures and qualities of Penicillins X and G, and of ampicillin were part of the relevant common knowledge. Because of the success of ampicillin it would be taken as the lead compound by the ordinary antibiotic or penicillin chemist. Penicillin G, because of its success and also having a naked phenyl ring, would also afford a useful guide for making substitutions on the latter. Having regard to the structure of Penicillin X (with the hydroxy radical attached to the phenyl ring in the para-position), he could easily therefore have taken the step of substituting the hydroxy radical on the naked phenyl ring of ampicillin. He would thereby achieve the products of the 1963 Patent, and in particular amoxycillin, the product of Claim 2 thereof, in which the hydroxy radical is in the para-position on

the .... /90

the phenyl ring, as with Penicillin X.

Both Professor Rinehart and Dr Menotti testified along those lines. But as the problem confronting the ordinary antibiotic or penicillin chemist is the discovery of new, different penicillins, would he choose ampicillin as the lead compound? That seems somewhat doubtful. But in any event it is most improbable that he would have looked to Penicillin G or X as any guide to the correct approach. For merely because they, or any other penicillin, had a structure resembling those of the 1963 Patent's compounds, that would not necessarily indicate, for reasons already given concerning small chemical, structural variations between different compounds, that their properties would be similar. Besides Penicillin X was not a successful natural penicillin: it was never marketed; and

like .... /91

like Penicillin G it was not particularly active against Gram-negative bacteria. Indeed, Dr Menotti did not even mention Penicillin X as any such guide until he was asked in cross-examination about it, when he then agreed with Professor Rinehart's suggested use of it. Moreover, although Penicillin X had an hydroxy substituent on the phenyl ring, none of the "preferred class" of compounds in the 1959 Patent had such a substitution. Nevertheless, both these witnesses said that such a substitution would have been done by tne hypothetical ordinary chemist because it was a well-known and very simple chemical step to take in preparing compounds. That may be, but that does not answer the question, why when that chemist is faced with the problem of discovering which of the hundreds of thousands of compounds of the 1959 Patent are active against Gram-negative bacteria, would

he .... /92

he immediately or easily choose those with the hydroxy substituent on the phenyl ring? The Court a quo rightly held that their evidence did not provide the answer to that question. Their difficulty, ever present in cases like the present one, was to avoid being wise after the already accomplished fact of the hydroxy substitution with its resultant desired activity. Professor Rinehart candidly conceded the problem of trying to project his mind 14 years back. But however much these witnesses tried to avoid hindsight both the Courts below correctly found that their approach was influenced by ex post facto reasoning. Bristol contended that the history of Beecham's alleged invention disproves such hindsight and confirms the correctness of their approach. That is unacceptable for reasons presently to be advanced.

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Of course, the postulated ordinary chemist when confronted by the problem, would probably resort to experimentation with various compounds in the course of which he might try the hydroxy substitution on the phenyl ring and test the results for activity against Gram-negative bacteria. But Dr Nayler, whose evidence was accepted in both the Courts below, said that, although the hydroxy was a fairly common organic radical, its substitution on the phenyl ring would not be tried as a matter of course; it might be tried "sooner or later, perhaps later, or might not be tried at all", depending upon the particular chemist concerned. And I emphasize here that the chemist concerned must not be regarded as being a person of exceptional skill, qualification, or knowledge or as having any inventive intuition or ingenuity. Hence, embarking on any such

experimentation .... /94

experimentation would really be setting out on a voyage of discovery rather than one of mere verification. That is precisely what the work of Dr Nayler and his colleagues in Beecham on the compounds of the 1963 Patent demonstrates. The facts are as follows.

In the evolvement of the compounds of the 1959 Patent Beecham took as its lead compound Penicillin N because of its activity against Gram-negative bacteria. It concentrated for partly the same reason on compounds with the amino groups in tne alpha position, for these, it had been found, were acid stable and that would improve such activity. The last of the 1959 compounds that it made and tested (November 1958) was the alpha-amino-benzyl penicillin, a DL mixture, AB 1060. It is the subject of Example 11 and Claim 8 of that Patent. Its

phenyl .... /95

phenyl ring had no substituent. This penicillin showed much promise in activity against Gram-positive and Gram-negative bacteria. Beecham was therefore encouraged to pursue its search for better and different penicillins. Between November 1958 and June 1962 it experimented, made, and tested a variety of some 12 compounds. Penicillin N was still the lead compound with AB 1060 as a supplementary guide. Apart from that, the experimentation did not follow any pattern. During this time too the separate D and L epimers of AB 1060 were resolved. The D compound, AB 1341 (January 1960), was ampicillin, and the L compound was AB 1394. Neither of the natural penicillins, G or X, played any role in those experiments. Some, but by no means all, of those compounds had different substitutions on the phenyl ring, but not the hydroxy substituent. True, it appears

from .... /96

from two of Beecham's documents of March and June 1959 that, among many other prospective experiments, it contemplated preparing alpha-amino-benzyl compounds with hydroxy substituents on the phenyl ring as being "of potential interest for use against Gram-negative organisms". But the only experiment carried out was unsuccessful. It was not repeated until June 1962, when AB 1886, the first compound (a DL mixture) of the 1963 Patent was successfully made and tested. Its promising activity against Gram-negative bacteria led to the further DL compounds, AB 1951 and 1953, being made. On the results of these 3 compounds that Patent was applied for and granted. The resolution of their D and L epimeric compounds followed later.

That history refutes the correctness of the approach of Professor Rinehart and Dr Menotti and tends to

confirm .... /97

confirm that their evidence must have been influenced by hind-

sight. For while Beecham did rely partly on AB 1060 (the fore-

runner of ampicillin) as a lead compound, neither of the natural

Penicillins X or G, played any part in its investigations;

it used Penicillin N, as being "a unique pointer" to compounds

with activity against Gram-negative activity. Incidentally

it was not proved to be common knowledge that this natural

penicillin had that particular property and thus would have been

used as a lead compound by the ordinary skilled chemist.

Moreover, it is clear from that history that it was not obvious

to Beecham that putting the hydroxy substituent on the phenyl

ring was the solution to the problem. Otherwise, why did it

first try other substituents? And if it was not obvious to

Beecham with the highly skilled, inventive Dr Nayler, it would

surely .... /98

surely not have been obvious to the ordinary skilled and uninventive chemist. That the hydroxy substitution, together with many other experiments, were merely put on Beecham's lists for investigation tends to confirm its non-obviousness. The same applies to the lists of Dr Cheney. He was Bristol's chief chemist. In 1961 and 1962 he included a para-hydroxyphenyl derivative of AB 1060 on the lists of many compounds for experimentation. He did not, however, in fact make that derivative. That too tends to indicate its non-obviousness. Dr Cheney did not testify to prove the contrary.

The arguments of counsel for the parties also covered other points. It is unnecessary to deal with them because I have said sufficient to indicate my agreement with the conclusion of the Court a quo that Bristol did not prove that Beecham's invention was obvious and therefore not inventive. Indeed,

I agree with Beecham's final submission that the invention was made only after much empirical experimentation which also showed some scientific intuition and ingenuity, for example, in the perception of Penicillin N as a guide compound and the choice of the line of development that led ultimately to the first compound of the 1963 Patent, AB 1886, being made.

Selection Patent

To round off the issue of obviousness I should say something about Bristol's argument based on the conditions for validity of selection patents enunciated by MAUGHAM J. (as he then was) in the case of I.G. Farbenindustrie A.G.'s Patents (1930) 47 R.P.C. 289. By a "selection patent" the learned Judge meant (p. 321, l. 7) a selection of related compounds such as the homologues and substitution derivatives of

the .... /100

the original compounds described in general terms and claimed in the originating patent (here the 1959 Patent). The conditions enunciated are (p. 322, l. 45):

> "First, a selection patent to be valid must be based on some substantial advantage to be secured by the use of the selected members .... Secondly, the whole of the selected members must possess the advantage in question. Thirdly, the selection must be in respect of a quality of a special character which can fairly be said to be peculiar to the selected group."

The learned Judge made it clear that a selection patent does not in its nature differ from any other patent (p. 322, l. 42).

The reason, according to the case of Esso Research and Engineering Coy.'s Application for Revocation of Shell's Patent (1960) R.P.C. 35 (CA) at p. 53, l. 50, is that there is nothing in the English Patents Act which would justify such a differentiation and the above requirements are merely an exposition of the appli-

cation .... /101

cation of general patent law to that particular kind of patent.

In support of its case on obviousness Bristol contended that the 1963 Patent was a selection patent and did not comply with any of those conditions. It is unnecessary to decide whether, or to what extent, those conditions apply in our law. I shall assume, without deciding, in Bristol's favour that they do apply and that the 1963 Patent is a true selection patent. The essence of inventiveness of such a patent in our law would be the discovery (i.e., the further step) tnat "the selected members" all have some substantial, special, peculiar advantage over the other, unselected members that was not obvious having regard to what was common knowledge at the effective date. It is the latter feature that distinguishes "the selection" from being mere verification resulting "from the systematic

investigation .... /102

investigation or research" into the compounds of the originating patent (see the Farbenindustrie case (pp. 321, l. 6-26; 322, l. 12-37). In the present case, for reasons already given, the 1963 Patent complied with those requirements, or at any rate, Bristol, on whom the onus of proof rested, failed to prove the contrary. Put more specifically: Bristol failed to prove that the 1963 Patent did not comply with the Maugham conditions.

Before saying why, I must expand a little on the third condition. MAUGHAM, J., explained it at p. 323 l. 16. He concluded as follows (my interpolation in parenthesis):

> "The quality must be of a special character. It must not be one which those skilled in the art will expect to find in a large number of the (unselected) members."

For reasons already given, it was not part of the common knowledge as at 2 November 1962 that all or any particular number of the

unselected .... /103

unselected compounds of the 1959 Patent were active against Gram-negative bacteria. Nor, for reasons already given, was it proved that those few compounds of the 1959 Patent that were tested for such activity were representative of its other untested and unselected compounds, let alone that that or the results of those tests were then common knowledge. Consequently, the fact that all the selected compounds of the 1963 Patent had the desirable property of being active against Gram-negative bacteria, which all the unselected compounds of the 1959 Patent were not commonly known or proved to have, constitutes a fulfilment of the first and second conditions: it was a substantial advantage which all the selected compounds possessed. As to the third condition, it was a quality of a special character peculiar to the selected 1963 group, for Bristol did not prove that such quality

was .... /104

was possessed by a large number of the unselected compounds, let alone that the ordinary skilled penicillin chemists would expect them to possess it.

The appeal in respect of the issue of inventiveness must therefore fail.

For all those reasons the appeal is dismissed with costs, including those relating to the employment of three counsel.

W.G. TROLLIP, J.A.

CORBETT, J.A.)
MILLER, J.A.) concur
VILJOEN, J.A.)
GALGUT, A.J.A.)

SCHEDULE OF TESTS' RESULTS.

A. 1963 Patent.

AB Number	Date made or tested	Compound	Epimer Form	No. of Claim	MICs		CD_{50}s			
					ESCH. COLI	SALM. TI.	KLEBSIELLA PNEU.		SALMONELLA TYPHIMURIUM	
							Subcutaneous	Oral	Subcutaneous	Oral
1886	June 1962	para-OH	D+L	2	12.5	5.0	13,13,and 18	8;8;.8.6	3.2,<6.25to8.6	5.6,<6.5to 13
1951	Aug. 1962	meta-OH	D+L	3	12.5	5.0	13.0	8.0	5.6and 12.5	4.6and 23.0
1953	Aug. 1962	ortho-OH	D+L	1	50.0	25.0	> 100	> 100	27	92
2204	End 1963	meta-OH	L	3	25.0	12.5	> 400	> 400	> 100	> 100
2205	End 1963	meta-OH	D	3	5.0	1.25	8.5 to 19.0	2.1 to 12.5	3.2 to 5.7	3.2 to 12.5
2333	Oct..1964	para-OH (amoxycillin)	D	2	5.0	1.25	5.2 and 3.2	6.7 and 3.2	1.0 and 3.2	8.0 and 8.0
2374	1964	para-OH	L	2	25.0	12.5	200	135	72	>100
20088	Tested 1976	ortho-OH	L	1	125	50	Never performed		Never performed	
20089	do	ortho-OH	D	1	12.5	2.5	Never performed		Never performed	

B. Some of the 1959 Patent Compounds

1060	Nov. 1958	no OH Substituent	D+L	8	12.5	1.25	50 and 62	12.5	50 and 35	32 and 80
1341	Jan. 1960	Ditto (Ampicillin)	D	8	5.0	0.62	5.7 and 13 to 50	6 to 26	5.6 to 27	6.8 to 23
2113		Methylcysteyl	D+L	?	500	125				
2113A		Ditto	D+L	?	125	50	> 100	> 400	370	135
2229		meta or para - Dibenzyloxy	D+L	?	> 500	> 500				